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Thesis

EVIDENCE FOR SENSORY INNERVATION OF THE BLOOD VASCULAR SYSTEM

by

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(B.S., Providence College, 1943)

Submitted in partial fulfilment of the
requirements for the degree of
Master of Arts
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- I N T R O D U C T I O N -

The sensory innervation of the blood vascular system has for many years furnished problems for numberless investigations. Kölliker (1863) was one of the first observers to speak of sensory fibers innervating blood vessels. Since that time, a great deal of evidence, both anatomical and physiological has been presented.

The most difficult problem that has arisen in tracing myelinated nerves, both sensory and motor, to their terminations in blood vessels, is that of discovering proper staining methods for differentiating minute nerve endings from connective tissue fibers. With present staining methods, investigators have been able to trace sensory fibers to the walls of arteries, veins, and to the smallest arterioles and venules. They have however, not been able to follow the nerve endings to capillary walls.

It is the purpose of this study to combine and review the literature of the experimentations and observations on the sensory innervation of the blood vascular system, and its various reflex mechanisms. This review includes the most modern physiological concepts.

I. THE AXON REFLEX AND ANTIDROMIC CONDUCTION

In the presentation of evidence for the sensory innervation of the blood vascular system, mention must be made of the possibility of an axon reflex. The axon reflex is a local reflex involving dilation of skin vessels confined to the region of stimulation.

The term "axon reflex" was originally introduced by Langley and Anderson (1894). They divided the nerves going from the sympathetic chain to the inferior mesenteric ganglion in the cat, leaving intact the hypogastric nerves to the bladder. After dividing the left hypogastric nerve, they stimulated the central end and obtained a contraction of the right half of the bladder. Langley (1900) showed that this was not a true reflex. A preganglionic fiber arriving at the inferior mesenteric ganglion branches, one branch ending around the cells of the ganglion, the other branch passing down in one hypogastric nerve to a cell situated near the base of the bladder. Therefore, when the central end of the divided nerve was stimulated, the stimulus was actually applied to preganglionic fibers. The impulse was conducted to the point of junction of the two branches and then down the other branch to excite the cell in the

inferior mesenteric ganglion. Langley and Anderson thus obtained an apparent reflex by stimulation of a nerve which is motor. Figure I illustrates Langley and Anderson's explanation of this reflex.

Blood vessels dilate during the initial stages of acute inflammation. This dilation may be the result of an axon reflex involving a sensory nerve fiber. Bruce (1913) stated that the dilation of vessels in the conjunctiva of the rabbit in the initial stages of inflammation, resulting from application of mustard oil, is not affected by total section of the spinal cord. The vasodilation is also not affected by section of the posterior roots central to the dorsal root ganglia, nor by section of the sensory fibers peripheral to the dorsal root ganglia. This will hold true only if the severed peripheral part of the fiber has not degenerated. If the fiber has degenerated, or if the part to which the irritant is applied is under the influence of a local anesthetic, the vascular changes do not follow the application of the irritant.

Bruce was dealing with a reflex path, composed of an afferent sensory branch and an efferent vasodilator branch. He blocked the path by severing the nerve and waiting for degeneration, or by paralyzing the nerve endings with a local anaesthetic. Application of an irritant no longer produced

vasodilation following this obstruction. Total section of the spinal cord, or division of the posterior nerve roots central to the dorsal root ganglia did not abolish the reflex or interrupt it in any way. Consequently a nerve center for this reflex could not be located either in the spinal cord or central to it. The reflex effect was not altered by division of sensory fibers peripheral to the dorsal root ganglia. Therefore, impulses producing this effect need not pass as far centrally as the posterior root ganglion cells from which the sensory fibers arise. The reflex path under these circumstances is confined to the peripheral fiber.

Bruce assumed that if a sensory nerve fiber conveys impulses toward the periphery as well as toward the center, it must have peripheral motor terminations. In other words, as the fiber approaches the periphery it divides like a letter Y. One branch passes to sensory terminations in the skin. Afferent impulses pass along this fiber. The other branch ends in the blood vessels and motor impulses pass along this fiber. There must be a reflex action limited to these two branches. The reflex commences with stimulation of the sensory end, and results in a local vascular dilation.

Woollard (1926) traced myelinated sensory fibers along the anterior tibial artery of the cat from which the abdominal sympathetic nerves had been removed. He followed

collateral nerve fibers for a distance of an inch and described endings in blood vessels, and adjacent adipose and connective tissue. Woollard's study of the collateral endings has led him to believe that he has found an anatomical basis for the axon reflex.

Lewis (1927) stated that the sensory axon reflex is not witnessed on the surface of the human abdominal viscera. It is a mechanism peculiar to superficial and sensitive structures, such as the skin and conjunctival sac.

Bayliss (1900-1) demonstrated that if the posterior nerve roots of the dog are divided central to their ganglia, and the peripheral ends are stimulated, vsodilation occurs in the limb of the same side. The response is the same whether the stimulus be mechanical, electrical, chemical, or thermal. The fibers which conduct these impulses do not pass into the sympathetic chain since the vasodilation is still present after removal of the abdominal sympathetic chain. There are no white rami below the fourth lumbar ganglion, and there are no efferent fibers from the cord in the gray rami. Bayliss divided the lower lumbar and first sacral posterior roots in dogs as near as possible to the spinal cord. After two weeks the animals were anaesthetized and the nerve roots were stimulated. Vasodilation occurred in the vessels of the hind limb. Bayliss concluded that the vasodilator fibers of the posterior roots do not degenerate

on section between the posterior root ganglia and the spinal cord, and are therefore, not spinal efferent fibers. Bayliss extirpated the spinal ganglia on one side of the dog from the fourth lumbar down to the second sacral. He stimulated the cut peripheral ends of the two sciatic nerves on the ninth day following the operation. Mechanical or electrical stimulation produced only vasoconstriction on the side of the lesion. Bayliss observed no trace of dilation on the side of the lesion, even after constriction had closed off. He concluded therefore that all the vasodilators had degenerated, and that if the vasodilation in the hind limb is produced by excitation of vasodilator fibers the impulses must pass down posterior root fibers.

The vasodilator response obtained by Bayliss (1900-1) may be explained on the basis of antidromic conduction. Presumably, impulses are conducted by the sensory fibers toward the periphery in a direction opposite to the usual direction. The axon reflex described by Bruce (1913) probably involves antidromic conduction. For example, local irritation may stimulate sensory endings and result in central conduction of impulses to the point of bifurcation of the fiber, and peripheral conduction to the blood vessel.

In figure II, it can be seen that the impulses which arise from the central nervous system, and pass peripherally by way of the posterior root ganglia, will cause a dilation

of the blood vessels. The dilation is exactly the same as that produced by mustard oil after severing the peripheral nerve above the bifurcation in order to limit the reflex path to the two branches peripheral to the bifurcation. The reflex mechanism as described by Bruce (1913) is the most primitive reflex possible, being limited to the branchings of a single nerve fiber. It does not involve a nerve cell, and has no synapse. It is a true "axon reflex."

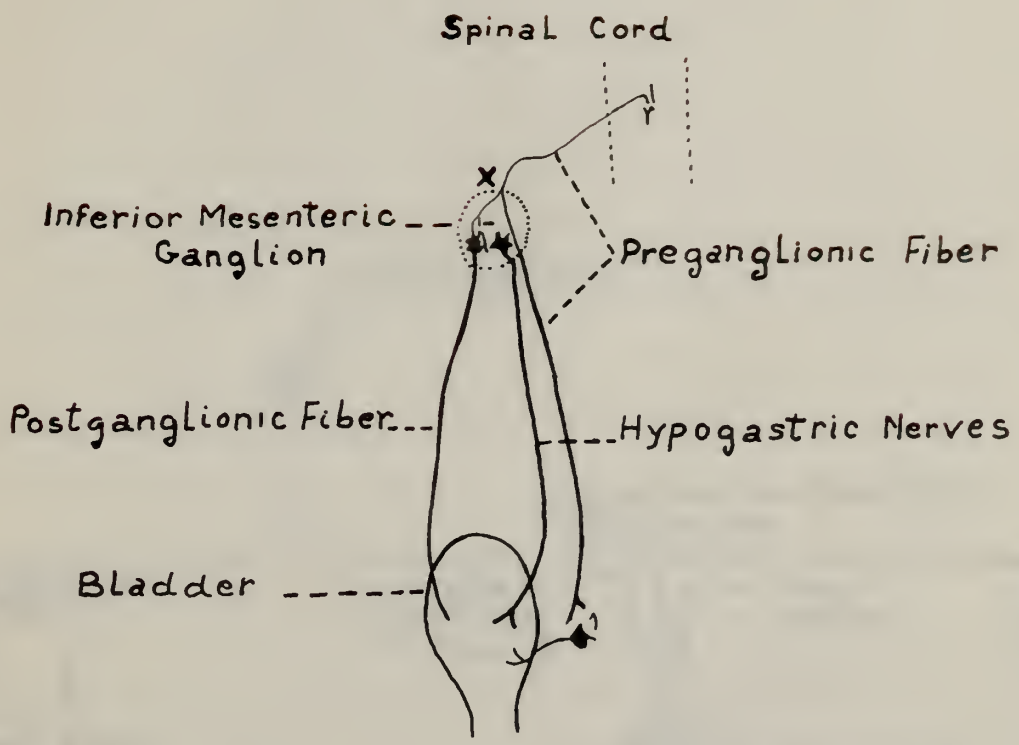
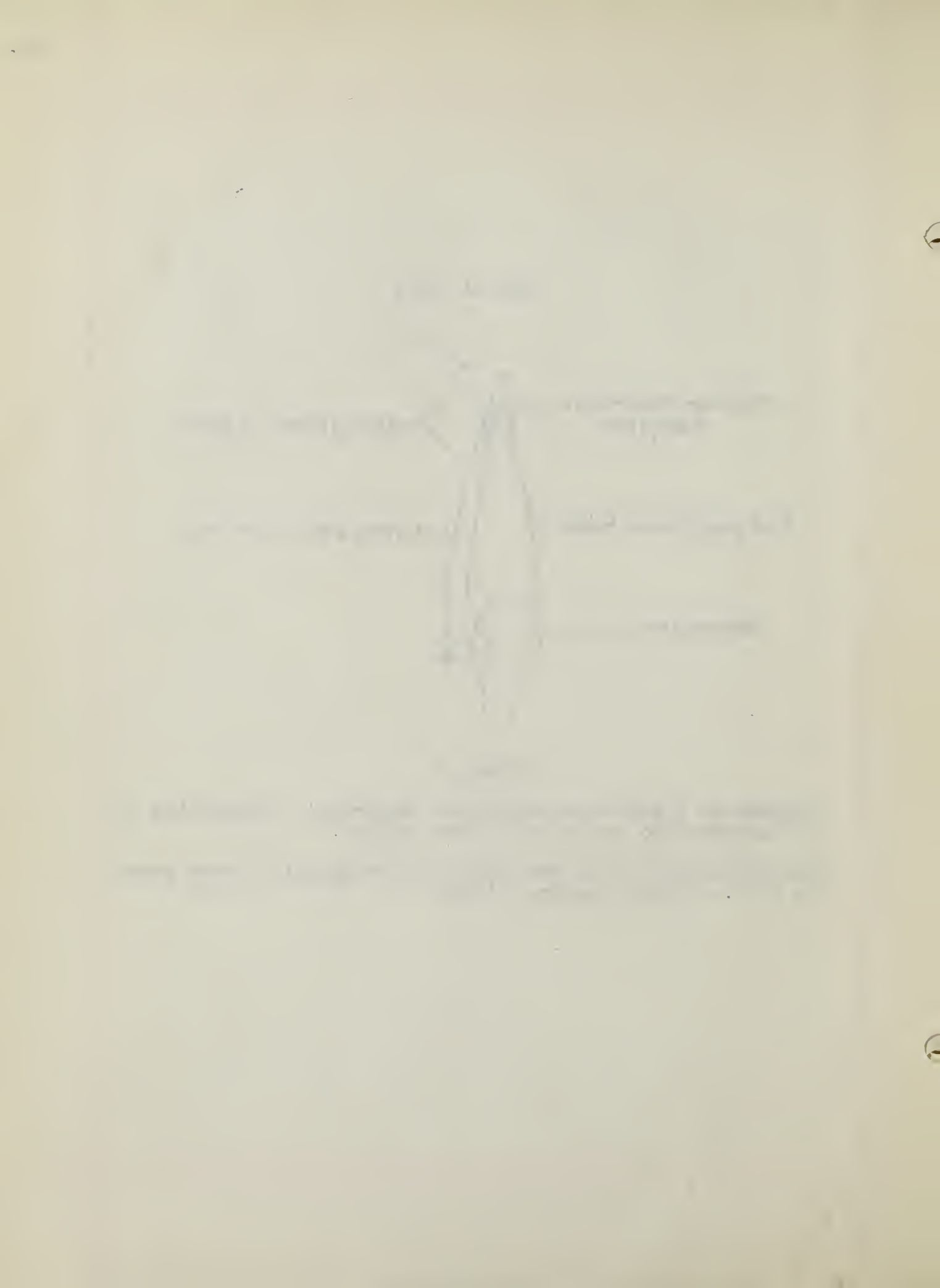


Figure I

Diagram to illustrate Langley and Anderson's explanation of the hypogastric reflex as an axon reflex.

The branching of the axon where the propagation takes place is at X. - After Starling (1941)



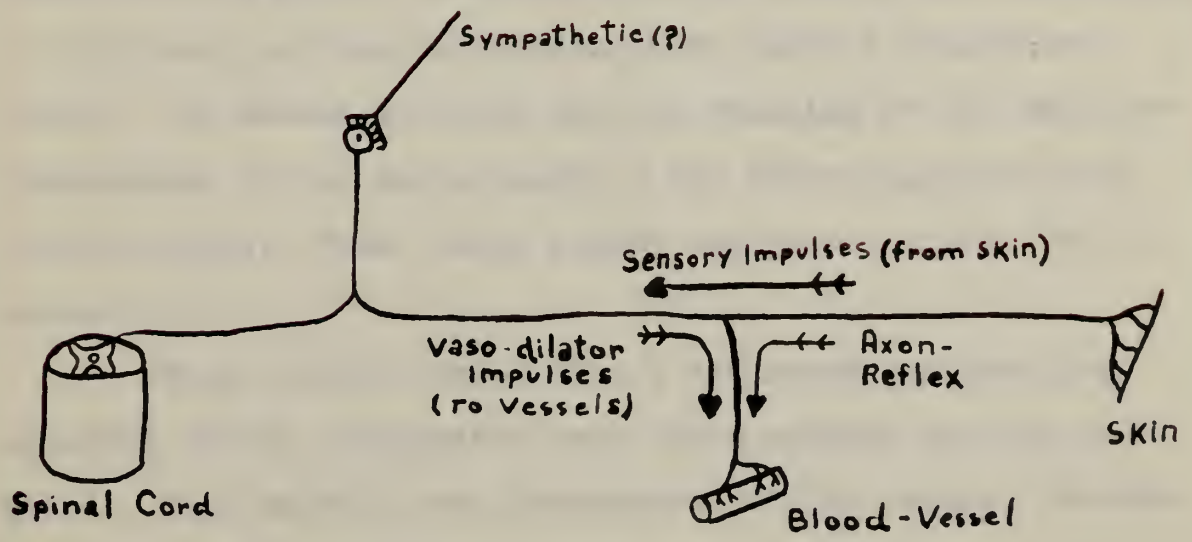


Figure II

THE AXON REFLEX - Bruce (1913)

II SENSORY INNERATION OF BLOOD VESSELS IN VARIOUS TISSUES AND ORGANS

A. Blood Vessels of the Skin

A triple vascular reaction normally follows a localized injury to the skin. The blood vessels dilate, the skin wheals or blisters, and the surrounding skin shows a bright red flare. The vessel dilation and the whealing of the skin are independent of the nerve supply. The flare reaction is of reflex origin. These three events are known as the "triple response."

Bruce (1910) showed that a reddening and swelling occurred in the conjuctival sac, after mustard oil was applied. This reaction was independent of the central nervous system, and took place after the sensory nerves to the conjuctiva had been divided. Bruce concluded therefore, that the inflammation was due to a local axon reflex. Lewis and Grant (1924) and Lewis, Harris and Grant (1927) observed that anaesthetized skin when scratched with a needle yielded a fine red line. When anaesthetized skin was stroked, a red band was produced. A hot test tube when applied yielded a small circular red spot. Each of these reactions was surrounded by a red flare due to dilation of arterioles. When the reflex arc to the spinal cord was interrupted and its

sensory limb separated, the vascular reactions of the skin to many types of stimuli remained unchanged. Reactions of skin to which nerves had degenerated were much different. None of these stimuli produced a surrounding flare.

Lewis (1927) stated that the local red reaction is entirely independent of nerve mechanisms, while the flare on the other hand, is of nerve origin and depends not upon the spinal reflex arc, but upon a purely local nerve mechanism. In addition to the axon reflex, the blood vessels of the skin are also regulated by local and general reflexes.

Lóven (1866) stimulated the cut central end of the posterior auricular nerve of the rabbit, and observed a dilation of the ear vessels. Similar reflexes in which vasodilation occurs in an area localized about the point of stimulus are known as "Lóven reflexes." These local reflexes, according to Bayliss (1923), take place partly by activation of vasodilator nerves which have their pathway in the antero-lateral region of the spinal cord, and partly by inhibition of vasoconstrictor impulses.

Fulton (1947) explained the function of the local vasodilator mechanism as repair of local injury. The general reflexes give rise to general vasoconstriction. The vasoconstrictor nerves are practically all sympathetic. The afferent pathway lies in the apex of the posterior horns.

From the central portion of somatic nerve trunks, sympathetic fibers pass to the main blood vessels; and from the peripheral portion, sympathetic fibers pass to the smaller arterioles. General vasoconstriction is a reflex response to stimulation of the central ends of sensory nerves. The general constriction is a part of the response to emergency.

Finally, cutaneous vessels may be innervated by sensory nerves which conduct antidromically. Bayliss (1900-1) considered the posterior root system as the only supply of vasodilator nerves to the limbs. The sensory nerves carry the impulses antidromically, and reach the cutaneous vessels through sensory nerve branches. Woollard (1926) traced the sensory fibers peripherally. They were seen to give off collaterals. The collaterals end in terminations in the adventitia of the walls of the arterioles. They also end in the surrounding fatty connective tissue, and in Pacinian corpuscles. He presumed that they also ended in the skin.

These results do not prove that normally, impulses are carried along these paths from the central nervous system to the peripheral vessels. Thus, physiologists have experienced difficulty in relating the concept of antidromic conduction to the classical concepts of nerve condition.

Lewis and Marvin (1927) using the forepaw of the cat, investigated the sensory innervation of the skin. They excised the stellate ganglion sometime before the experiment, interrupting the sympathetic pathway to the blood vessels and sweat glands. They assumed that the sympathetic elements had degenerated. They stimulated the branches of the median (sensory) nerve, and obtained vasodilation which they explained on the basis of antidromic conduction. They observed that brief faradic stimulation produced a long lasting dilation. They recalled that when vasoconstrictor nerves are stimulated, the reaction comes quickly and subsides quickly after the stimulation is stopped. A second observation showed that the response is often related to the duration of the stimulation. Lewis and Marvin's third observation was on human skin. They detected no vasodilation when the circulation of the limb was arrested.

Lewis (1927b) suggested ".... that the antidromic impulse liberates a vasodilator substance in the skin during circulatory arrest that is held there until the release, and that it is then gradually removed. The antidromic nerve impulse affects metabolism in the cells of the skin, causing release of a vasodilator substance." Lewis attempted to explain herpes zoster, a skin reaction correlated with a lesion in the posterior root ganglion on this basis. Herpes zoster

is an erruption, with severe pain, and reddening and swelling of the skin over an area corresponding to the distribution of a sensory root. Lewis believed that herpes zoster was due to this vasodilator substance which he termed (H) substance. Much more research must be done in this regard.

B. Blood Vessels of the Kidney

According to Kuntz (1947) the kidney is innervated mainly by way of the renal plexus. This plexus extends from the aortic plexus to the hilum of the kidney along the renal artery. It is made up of rami from the celiac ganglia, fibers from the aortic plexus, and joined by branches from the lesser splanchic nerve fibers from the vagus. The afferent fibers are mainly components of the tenth, eleventh, and twelfth thoracic nerves.

Renner (1924) described myelinated nerve fiber terminations in the kidney. Innervation of the renal vessels was observed in the musculature of the renal pelvis, the calyces, and the renal capsule.

Kaufman and Gottlieb (1931), using the intravital methylene blue and Bielschowsky's silver staining methods, studied sections of kidneys from rats, guinea pigs, cats, dogs, and man. They observed dense plexuses of myelinated fibers in the adventitia and medial layers of the arteries

and veins. The terminations were reported on arterioles and occasionally fibers were seen branching off into fibrous tissue.

C. Blood Flow to the Viscera

The blood flow to the viscera is controlled in essentially the same fashion as blood flow to the skin. Myelinated visceral afferent fibers have been seen in association with blood vessels of all the viscera.

Lawson and Chumley (1940) showed that if a loop of small intestine in the dog is stretched by overfilling, the blood flow is maintained in spite of the increased interstitial pressure. Further, if a strip of intestine is simply stretched transversely, it will cause increase in flow through the strip. They suggested as a working hypothesis, that stretching the walls of the intestine during inflation produces vasodilation through intrinsic nerve mechanisms, resulting in local circulatory compensation for the added resistance to flow.

Segmental reflexes of the Lóven type may also play a role in the control of visceral blood flow. The vasomotor centers of the central nervous system exert a control upon the visceral blood flow in the regulation of the general blood pressure. Because of the depressor responses obtained from the glossopharyngeal, vagus,splanchnic, and depressor nerves,

one might assume that afferent impulses arising in the viscera are more likely to cause a drop in blood pressure than those coming through somatic nerves.

Ranson (1921) described an experiment by Miller (1911) which showed that vasoconstrictor responses can be obtained from certain visceral nerves. Miller stimulated the central end of the gastric vagus in anesthetized rabbits and produced a rise in blood pressure. Ranson (1921) also described an experiment conducted by Dmitrenko (1916) who found that inflation of a rubber balloon in a dog's stomach was followed by a reflex rise in blood pressure.

Burton-Opitz (1917) showed that the vasomotor reflex from the splanchnic nerve closely resembles that from the depressor nerve in the rabbit. Working with dogs anesthetized with ether, he stimulated the central end of the splanchnic nerve and it caused a marked fall in blood pressure. He regards the splanchnic nerve as the depressor nerve for the abdominal viscera. In the cat, stimulation of the central end of the splanchnic nerve causes a rise in blood pressure. In the dog, stimulation of the central end of the vagus causes a rise in blood pressure, while a fall is obtained when the central end of the splanchnic is stimulated. In the cat a fall is obtained from the vagus, while the splanchnic gives a rise. The question as to whether these reflex vascular responses are initiated by

impulses traveling over sensory fibers terminating in blood vessels, presents a problem for further investigation.

Gammon and Bronk (1935) working on cats, demonstrated Pacinian corpuscles in the mesentery innervated by the splanchnic nerves. They believed that these corpuscles are receptors which are functionally related to the circulatory system. Pacinian corpuscles were found in great abundance along the arteries, the arterial branches to the mesentery, and along the arteries supplying the intestine. The corpuscles have an intrinsic circulation of their own. It had previously been shown that the corpuscles are excited by pressure or mechanical deformation. The corpuscles may be stimulated by elevating intravascular pressure either within the intrinsic vessels of the corpuscles or within the larger vessels which the corpuscles adjoin. Gammon and Bronk have not entirely eliminated the possibility that other types of endings in this region also discharge impulses synchronously with the pulse. The reflex effects of the Pacinian corpuscle receptors remain to be demonstrated.

D. Blood Flow Through the Liver

Berkeley (1893) using Golgi staining preparations observed in cats, amphibia and small mammals that the blood vessels of the liver are innervated mainly by nerves from

the celiac plexus and the vagi. As the hepatic artery and portal vein enter the liver they are accompanied by nerves made up mainly of unmyelinated fibers, and a limited number of myelinated fibers. Berkeley pointed out that the nerve supply to the hepatic artery is more abundant than that to the portal vein.

Alexander (1940) observed that the intrahepatic nerves of mammals consist mainly of unmyelinated fibers and a few myelinated fibers. He believed the myelinated fibers were probably visceral afferent. These afferent fibers were seen to be closely associated with the blood vessels. Alexander conducted experiments in which he cut the vagus nerves and waited for degeneration. No change in the number and distribution of nerve fiber was produced, except in the hepatic portal area. In this portion the myelinated fibers were reduced in number in some of the nerves which accompanied the blood vessels and bile ducts.

E. Blood Supply to the Muscles

Kölliker (1863) was one of the first observers to report sensory fibers innervating blood vessels. He observed them in the adventitia of blood vessels in frog muscle which was supplied by a branching myelinated fiber. Heidenhain (1878) suggested that stimulation of practically any sensory

nerve would cause a dilation of muscle vessels. He stimulated the radial nerve of the frog, and the vessels of the thigh dilated. Hinsey (1928) cut the sympathetic nerve supply to the vastus medialis of the cat and produced degeneration. He observed sections stained with a pyridine-silver method, and saw myelinated fibers give rise to fine unmyelinated branches. A single unmyelinated branch passed to an arteriole, and ended as far as could be traced, in the adventitia of the arteriole. He observed a few fibers terminate in the region of the arteriole-capillary junction. Hinsey observed a coarse unmyelinated branch of a small myelinated fiber situated in the wall of an arteriole. He saw it course through adipose tissue and branch for some distance in the adipose tissue. Fibers of this type had no differentiated endings. Hinsey believed that in as much as the dorsal roots were cut close to the cord, these fibers were derived from the posterior root ganglion cells and passed with the spinal nerve to eventually reach the blood vessels of the muscle.

F. Blood Flow Through the Uterus

According to Kuntz (1947) an abundance of nerve fibers has been observed in mammalian muscle and along the blood vessels. There is, however, no literature on the course of these fibers in the myometrium, with the exception of the

work done by Hirsch and Martin (1943) on the human uterus. Hirsch and Martin recognized myelinated fibers in nerve trunks of the uterus. They studied serial sections stained with a trichrome method. In observing the distribution of these nerves in the myometrium, small ovoid structures were found to extend a short distance from the main nerve trunk into the muscle tissues and into the adventitial casts of the branches of the uterine artery. In their search for sensory end organs, Hirsch and Martin believed these structures to be corpuscles of the Vater-Pacinian variety. Terminations of these myelinated (sensory) nerves were also seen to connect with a series of radial arteries. Many small branches supplied blood vessels and muscle tissues, although their ultimate endings were not determined.

G. Blood Flow Through the Lungs

Larsell (1921) observed sensory terminations in the adventitia of the pulmonary arteries in the rabbit. He was able to find these endings near the base of the artery only, close to the hilum of the lung. These terminations are connected with large myelinated fibers which may be traced to the sensory endings in the bronchi. Larsell having carried out experiments on mammals, supports the view that most of the nerve supply to the pulmonary vessels is sympathetic.

H. Blood Vessels in the Spleen

The extrinsic nerves approach the spleen by way of the plexus on the splenic artery. In the cat there are several splenic arteries. The afferent components of the splenic nerves are myelinated fibers which travel over the splanchnic nerves. Kuntz (1947b) found that in man, myelinated nerves enter the spleen through the hilus, and travel into the spleen along the arteries. According to Kuntz, Utterback (1944) counted the splenic nerve components of the cat and indicated approximately 2000 unmyelinated and only 110 myelinated fibers, a ratio of approximately 20 to 1. The spleen therefore, is supplied with very few afferent fibers, which are myelinated visceral afferents.

As the arterial branches enter the pulp they are accompanied by slender nerve fibers. These fibers travel along the smaller arteries, and continue along to the arterioles. Kuntz also observed myelinated fibers accompanying the trabecular veins in the dog.

I. Circulation Through the Brain

Huber (1899) using methylene blue stained preparations of the pia mater of dogs, cats, and rabbits, observed large myelinated nerve fibers accompanying the blood vessels

at the base of the brain, the medulla, and over the cerebrum to the great longitudinal fissure. Huber stated that myelinated nerve fibers reach the vessels of the pia mater from two sources. The first is from a relatively large bundle of myelinated nerves which joins the middle cerebral artery just after it gives off the posterior communicating branch. The bundle divides into two branches. One branch joins the middle cerebral artery; the second joins the posterior communicating artery. The other source is from myelinated fibers which travel upward on the basilar artery until it divides into the posterior cerebral arteries. The bundles of myelinated nerves on the basilar artery are formed from nerves on the vertebral arteries. Fig. III serves to illustrate these statements. There are no distinct areas of distribution of the myelinated nerve fibers, accompanying the vessels of the pia mater and coming from the two sources mentioned. The bundles of myelinated nerve fibers on the vessels which form the anterior part of the circle of Willis are distributed to half the circle of Willis and to the arteries which arise from it, and in part, to the opposite sides of the circle of Willis. The myelinated nerves which enter with the basilar artery pass, at least partially, to the anterior part of the circle of Willis. The myelinated fibers undergo repeated division. The branching is observed mainly at places

where the artery divides. One branch of a nerve follows each arterial branch. A single sensory fiber may then be distributed over a large area. The myelinated fibers may also be seen parallel with the branches of the anterior and middle cerebral vessels.

Huber traced the myelinated fibers parallel with intracerebral vessels to the longitudinal fissures in dissections of the lateral aspect of the hemispheres. The myelinated fibers that accompany vessels of the pia mater appear as single fibers or as bundles consisting of two to five fibers, undergoing repeated division along the course of the vessels. The branches of the bundles or of the single fibers wind around the vessels and occasionally anastomose with each other. Large plexuses are formed which surround the vessels. The best nerve preparations were obtained in the cat, although the nerve terminations were similar in the dog and rabbit.

In the posterior cerebral artery, a myelinated fiber, after reaching the vessel, gives off several large myelinated branches. These branches leave the main fiber at nodes of Ranvier, where they divide into small myelinated fibers, which in turn divide into small ones. The myelinated branches terminate in unmyelinated terminal fibrils. The fibrils travel some distance before then end in small granules or nodules. Huber (1899) observed these terminal endings in all

parts of the pia mater of the cerebral hemisphere. Sometimes it is too difficult to trace them for distances long enough to discover their origin. The nerve bundles of myelinated fibers and most of the single myelinated fibers are situated in the adventitia of the vessels. Most of the terminal fibrils of the myelinated nerves end in the adventitia of the vessel or in the surrounding connective tissue. No myelinated nerve fibers have been observed accompanying the veins of the pia mater. The veins of the pia have no muscular coat and are easily distinguished from arteries in which the muscle cells are readily stained.

Huber assumed that the myelinated fibers in the pia mater are sensory in function. He has based this assumption on histological appearances, the nature of the nerve endings, and their distribution. The axons of these myelinated fibers are much larger than axons of sympathetic neurons or of white rami. The myelinated fibers branch and rebranch. This is usually observed at sensory terminations. The non-myelinated endings of myelinated branches end in the adventitia of vessels or in the pia mater. The terminal branches run parallel to the vessels or cross them obliquely. They are unlike vasomotor fibers which end in the muscular coat.

In the human pia, Stöhr (1922) described numerous sensory nerve bundles, separate fibers and endings. He

found that the nerve fibers were most numerous in the pia over the base of the brain, and especially in the tela choroideae. They decreased in number toward the superior longitudinal sinus, were scarce on the medial side of the cerebral hemispheres, and were apparently lacking in the pia of the cerebellum. Stöhr suggested that these sensory nerves may be the afferent part of a mechanism regulating blood pressure and intracranial pressure, or that by their action headaches and other symptoms of intracranial pathology may be produced.

Alexander (1875) first described myelinated fibers accompanying the arteries of the dura of the dog, guinea pig, rabbit, rat, mouse, dove and frog. He also observed bundles of myelinated nerves having a course independent of the vessels, and saw no difference in the mode of ending between the myelinated nerves of the dura accompanying the vessels, and those having a course independent of them. In both cases the myelinated nerves, after repeated branching at the nodes of Ranview, lose their myelin and continue as unmyelinated fibers. These unmyelinated fibers end as long fibrils. The terminal branches interlace in every conceivable manner, appearing as a nerve plexus. There are, however, no anastomoses of the nerve fibrils. The myelinated fibers traveling along the arteries of the dura often terminate over them or in such a way as to surround the vessels. There are no perivascular

plexuses formed. No myelinated nerve ending has been traced to its final termination in the dura.

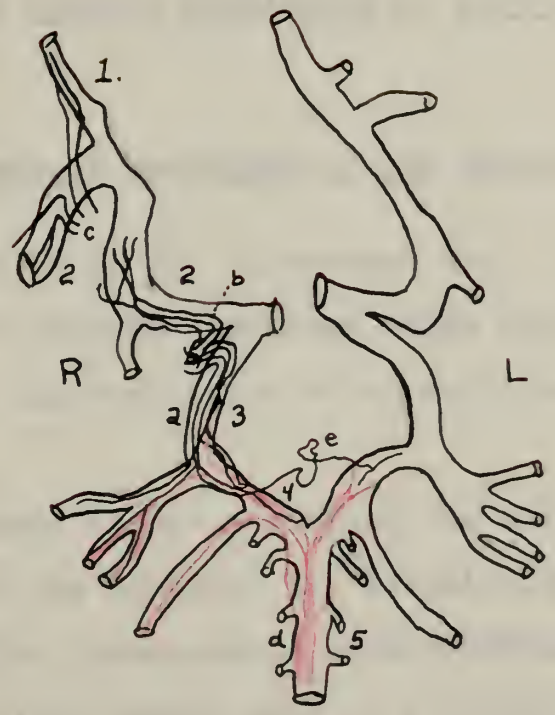


Figure III

CIRCLE OF WILLIS AND BASILAR ARTERY OF CAT SHOWING DISTRIBUTION OF SENSORY NERVE FIBERS

1. Anterior Cerebral 2. Middle Cerebral
3. Posterior Communicating 4. Posterior Cerebral
5. Basilar.

a. Myelinated nerves accompanying the posterior communicating branch. b. Branch containing ten myelinated fibers accompanying the middle cerebral. c. Continuation of b.

Huber (1899)

III SPECIALIZED SENSORY MECHANISMS OF LARGE BLOOD VESSELS

A. Sensory Mechanism of the Carotid Sinus

H. E. Hering (1927) discovered that the carotid sinus is the source of afferent impulses which exert important reflex effects in the regulation of circulation, and respiration.

Dautrebande (1934) described the structure of the carotid sinus in the rabbit. His description is illustrated in figure IV. The intercarotid nerve terminates in two branches. The first branch ends in a structure called the glomus caroticum, and the second in sensory fibers in the bulb of the internal carotid and the entire region of the carotid bifurcations. When these two branches unite they form the carotid nerve (nerve of Hering). This continues centrally to join the glossopharyngeal nerve. A few nerve fibers join the vagus ganglion instead of the glossopharyngeal.

The glomus caroticum is commonly called the "carotid ganglion." However, it contains mostly sensory nerve endings, and not ganglion cells. Therefore, carotid ganglion is an incorrect term.

Variations of the intrasinus pressure play a part in the regulation of the general blood pressure. Hypertension in this region produces general somatic hypotension with bradycardia, while a reduced intracarotid pressure results in general hypertension by means of peripheral vasoconstriction and tachycardia.

The sensory endings of the intercarotid nerve in the carotid sinus are extremely sensitive to pressure. This can be shown by recording the changes of blood pressure in the femoral artery, while varying the pressure of fluid perfusing the sinus endings of the nerve. An increase in the pressure of the sinus causes a fall of blood pressure and if the sinus pressure is decreased, a rise in blood pressure follows immediately. Hering (1927), Heymans (1938), and Schmidt (1932) have confirmed these findings by occlusion of the two common carotids, and by denervating the carotid sinus. Section of the nerve of Hering removes the depressor control, and brings about a state of chronic hypertension and tachycardia.

It should be brought out here, that any change in the pressure within the carotid sinus affects not only the blood pressure and heart rate, but also the respiration. When the general blood pressure is increased the respiration is increased. Denervating the carotid sinuses, or occlusion of the carotid arteries abolishes the inhibitory influence on the respiratory center, and there is a marked increase in

pulmonary ventilation.

Bronk and Stella (1932) observed that the nerve from the carotid sinus of the rabbit conducts impulses to the centers at all blood pressures, and that the number of impulses follows closely the changes in the arterial pressure during the heart cycle. Since these observations were made on normal living animals, Bronk and Stella came to the conclusion that this regulatory reflex is constantly functioning, and is not called into action only at supernormal levels of pressure. The continuous activity is brought about by a varying number of impulses conducted to the vasomotor centers per unit of time. Bronk and Stella believed that the alteration in the number of afferent impulses is effected by a variation in the number of end organs functioning at various pressures, by a change in the frequency of impulses discharged from the individual receptors, and by modifications from short bursts to a continuous succession of impulses. There is not very much known concerning the excitatory state of the vasomotor centers. Bronk and Stella have assumed that their activity depends upon the number and frequency of sensory impulses that are conveyed to them in a given time.

Lutz (1930) demonstrated that mechanical or electrical stimulation applied to various parts of the surface of the body and certain viscera produced cardiac and respiratory inhibition in elasmobranchs. Lutz and Wyman (1932) altered

the pressure within branchial vessels of Squalus acanthias by perfusion of the gills, and obtained inhibition of the heart. They stated that the cardio-inhibitory response was a reflex, having afferent pathways in the branchial nerves and efferent pathways in the vagus innervating the heart. Lutz and Wyman (1932a) observed reflex cardiac inhibition due to increased pressure in the ventral aorta of Squalus resulting from a spontaneous ejection reflex. Cardiac inhibition was associated with a decreased diastolic pressure in the ventral aorta. In Necturus maculosis reflex cardiac inhibition could be obtained only when the gills were stimulated by electrical or mechanical means (Lutz and Wyman 1932a). Lutz and Wyman concluded that the mechanism which effects cardiac inhibition in the elasmobranchs and Necturus may be compared with the carotid sinus mechanism of mammals. Since the carotid arteries of mammals are derived from the primitive branchiovascular system, they suggested that the reflex cardiac inhibition may be evidence for an evolutionary origin of the carotid sinus. Perhaps the carotid sinus mechanism may be evolved from a phylogenetic elasmobranch-like ancestor by delimitation of the widespread reflex areas to derivatives of the branchial arches.

B. Sensory Mechanism of the Heart

Most of the information on the innervation of the heart

has been obtained from studying lower animals. Dogs, cats, and rabbits have been used most extensively in detecting sensory endings in the heart. There have been very few studies of the human heart due to technical difficulties in tracing the distribution of the small nerve trunks and of the single nerve fibers.

A widely used method of studying nerve distribution in lower animals is that of staining the nerves with methylene blue as advocated by Ehrlich and described with some modifications by Woollard (1926a). The best results are obtained here by staining immediately after the death of the animal. It is impossible to meet these conditions in examining the human body. Many silver impregnation methods have been tried, but with these methods it is difficult to differentiate single nerve fibers from the surrounding connective tissue. A nerve fiber can scarcely be identified once it is separated from its trunk. Both connective tissue fibers and nerves are blackened.

The silver impregnation method of Cajal with modifications by Nonidez (1939) has some advantages for distinguishing the various nerve fibers. The parasympathetic postganglionic fibers are stained dark brown or black; the sympathetic postganglionic fibers, yellow or orange. The visceral afferents and preganglionic parasympathetics are also darkly stained by this method. The large nerve trunks of the heart can be stained by the usual methods and followed

in serial sections. These methods are inadequate for studying the finer nerve trunks, the single nerve fibers, and nerve endings.

Smirnow (1895) using a methylene blue technique in the auricles of dogs, cats, and rabbits, demonstrated a rich subendocardial plexus of afferent nerves. There is a similar plexus in the ventricles but it is not as compact. Dogiel (1898) showed similar structures appearing in the subepicardial tissues of the hearts of dogs, cats, and a child.

Woollard (1926a) studying the sensory innervation of the hearts of snakes, dogs, cats, and rabbits with a methylene blue stain, found all the nonmuscular tissues to be richly innervated. He found many fine nerve plexuses in the subepicardial and endocardial tissues as well as in the valves of the heart. These plexuses are composed of the finest fibers, which give off smaller branches. The fibers grow continually finer until they disappear. Woollard presumed that since these fibers innervate a portion of the heart that is nonmuscular, and have no motor function, they must be sensory in nature.

The fibers entering the above-named structures, are myelinated for some distance; then each fiber gradually loses its myelin sheath as it approaches its termination. The naked cylinder continues for a short distance and then breaks up into a complicated nerve ending which is large and is ex-

tensively branched and rebranched. A large number of filaments are produced which end in bulb-like expansions. It has been proposed that these endings have capsules.

Nettleship (1936) and others have shown that nerve trunks coming from the subepicardial region follow the route ofthe coronary arteries. Nettleship recognized three nerve plexuses in the heart. First, there are those located beneath the endocardium; secondly there are plexuses in the adventitia of the aorta and of the pulmonary artery; and thirdly there are those in the tissues that surround the coronary arteries.

Recently Hirsch and Orme (1947) reported some observations on sensory innervation of the human heart made from section studies.

In the subepicardial regions there are a large number of nerve trunks. Many of these trunks are located just below the serosal surface in the fibrous and fat tissues. Nerve trunks of different sizes accompany the branches of the coronary artery through the myocardial and subendocardial regions. Many times more than one nerve trunk accompanies an artery, and the position of the nerve in relation to the artery varies. Sometimes it is far removed, and is found in the loose areolar connective tissue, but other times it contacts directly with the adventitia of the artery.

The nerve trunks are often observed as branched,

following the artery as it divides. At other times, the nerve trunk passes from the artery, extends into the loose areolar tissue which is between bundles of cardiac muscle, and associates itself with another blood vessel. The size of the nerve trunks diminishes as they approach the endocardium.

The myelinated fibers of the nerves that are distributed along the coronary arteries of the heart are thought to be afferent, and therefore sensory in function. At this time, no conclusions have been reached as to whether these fibers are part of the vagus nerve, having their cell bodies in the nodose ganglia, or whether they have cell bodies in the d orsal root ganglia of the spinal cord and accompany the sympathetic nerves. The coronary arteries receive an exceedingly rich innervation.

The anatomical distribution of the sensory nerves of the human heart is extremely interesting because these fibers are transmitters of pain sensations. Pain occurs in heart abnormalities and some forms of heart disease. A few notable ones are angina pectoris, coronary occlusion and myocardial infarction. The myocardium is not sensitive but the sensory fibers of the heart do respond to painful stimuli. These sensory fibers are located in the adventitia of the coronary arteries. At short intervals they send terminal branches to the smooth muscle of the media. This suggests that the

painful stimuli in the heart arise in and about the coronary arteries rather than in the muscle tissues. That sensory fibers are distributed in the coronary arteries of the heart in a pattern similar to that of the peripheral arteries, provides an anatomic basis for this suggestion.

C. Sensory Mechanism of the Aorta

The sensory innervation of the aorta can best be explained by a detailed description of the aortic nerve (depressor nerve), and the distribution of the aortic afferent fibers.

Cyon and Ludwig (1866) discovered the depressor nerve in the rabbit. They named it "depressor nerve", because after sectioning it in the neck region, they stimulated it centrally and caused a fall in the blood pressure and a slowing ofthe heart beat. Nonidez (1935) said, "The term depressor is far from correct, for the nerve under consideration is primarily a bundle of afferent fibers mediating impulses, originated through changes in blood pressure, from the aortic territory to the nerve centers."

The reactions following stimulation of the aortic nerve are identical with those which occur when the nerve endings in the wall of the carotid sinus are mechanically excited. Reflex dilation in the case of the depressor or sinus nerve causes a fall in the blood pressure, while

increased blood pressure is caused by vasoconstriction.

Koster and Tschermak (1902) first traced the aortic depressor fibers to the aorta and the innominate artery. The right and left aortic depressor nerves of the rabbit break up into smaller bundles which form a plexus on the wall of the aorta. Most of the fibers were observed to be restricted to the adventitia, although a few were seen to enter the media. They were then unable to follow the fibers any further. There were no depressor fibers detected entering the heart, but there were some in the ascending aorta.

Tello (1924) using mouse embryos (4 to 18 mm.) and 17 mm. rabbit embryos, traced the development of the aortic nerve. A small bundle of sympathetic fibers that issue from branches which accompany the carotid, and from fibers from the stellate ganglion, enters close to the termination of the depressor nerve of the mouse. The left depressor terminates by encircling the aorta external to where the left carotid originates. The right aortic nerve is thinner than the left, and terminates around the base of the right subclavian artery.

In the rabbit embryo, Tello found that the right depressor ends in a rich arborization around the base of the right subclavian. Similarly the left depressor ends

around the aorta.

Nonidez (1935a) traced the aortic nerves of the adult rabbit and observed that each aortic nerve, as it approaches the artery on which it terminates, breaks into branches. These branches follow independent routes toward the artery. The "aortic glomus" is located in this vicinity.

The right aortic nerve ends around the base of the right subclavian. The greatest number of terminations are located in the superior posterior aspect of the artery. Some branches traveling along the externa reach the anterior portion. A few smaller branches terminate on the wall of the distal portion of the innominate artery. The left depressor of the rabbit is larger and has a greater area of distribution than the right nerve. Most of the sensory endings are found in the superior-posterior portion of the aorta medial to where the left subclavian artery originates. The anterior surface has very few endings; but the caudal aspect is very thickly innervated due to the fact that it receives sensory fibers from the left vagus in addition to the fibers from the depressor.

The fibers of the anterior branch of the left aortic nerve terminate by intermingling with endings from a bundle which leaves the vagus slightly above or below the point

where the left recurrent nerve emerges. Nonidez called it "the aortic branch of the vagus." This branch is associated with a group of cell cords of structure identical with those of the aortic glomus. The aortic branch of the vagus may anastomose with the anterior branch of the aortic nerve. This situation does not exist on the right side.

At the base of the left subclavian artery and nearly encircling it, are sensory fibers that emerge from the aortic nerve. The sensory fibers running in the left aortic nerve have a quite restricted distribution. The same is true of the right aortic nerve. The right and left aortic nerves furnish pressoreceptors to the branches of the arteries that supply the aortic glomera.

Outside of the area that marks the distribution of the left aortic nerve, no sensory endings could be found. This applies not only to the aorta, but also to the pulmonary arteries as well as the proximal portions of the coronary arteries.

The areas of distribution of the fibers of the right and left aortic nerves in the cat and guinea pig are identical with those of the rabbit.

Nonidez (1935a) stated that in the adult anatomy, the right aortic nerve is not really an aortic nerve because its fibers fail to reach the aorta. Embryologically

this can be explained by the fact that the proximal portion of the right subclavian is the persisting fourth (aortic) arch of this side of the embryo. Therefore, the presence of the right aortic nerve in adult mammals can be explained on the basis of the utilization of the right fourth arch. Should one of the fourth arches disappear while developing, there will be only one aortic nerve in the adult. Nonidez (1935b) explained that there is only one aortic depressor nerve in birds. The left fourth arch is not retained as the left subclavian. It develops from another source.

D. Sensory Mechanism of Large Veins of the Heart

In the superior vena cava the most abundant endings are found in the posterior medial aspect of the vessel just before it enters the right atrium. In the inferior vena cava the nerve endings terminate as a ring at the junction of the vein with the atrium. They extend somewhat into the wall of the atrium. The receptor areas of the pulmonary veins encircle the proximal portions of these veins and also occur in the posterior wall of the left atrium. There are also endings in the wall of the coronary sinus as it opens into the atrium.

Nonidez (1937) indicated that nerve bundles which are part of ganglionated plexuses are contained in the outer

coat of the wall of the intrapericardial portions of the venae cavae.

In the cat, according to Anufriew (1928) there is a ganglionated plexus in the posterior wall of the atrium between the openings of the venae cavae. There is another plexus in the anterior wall of the right atrium. A similar triangular plexus is located in the posterior wall of the left atrium. The plexus between the openings of the venae cavae is quite large and emerges in part from a branch of the right vagus above the point where the trachea bifurcates. The plexus in the right atrium is formed by a nerve from the right stellate ganglion. This nerve sends a branch to the tracheal plexus. The plexus in the left atrium arises from the left stellate ganglion through a branch receiving anastomosis from the left vagus. The plexus on the wall of the superior vena cava of the cat is a portion of the plexus that is located between the openings of the superior and inferior venae cavae. In the dog the plexuses of the superior vena cava are more extensive. The plexuses carry postganglionic fibers from the stellate ganglion and fibers from the vagus.

Anufriew (1928) observed that in microscopic sections, the plexuses of the superior vena cava of the cat are formed by anastomosing bundles of fibers of different sizes. They are situated in the outer connective tissue or externa. Pre-

ganglionic fibers are also represented as multipolar type neurons surrounded by pericellular baskets. The thick myelinated fibers run singly or in bundles which course among the myocardial fibers to the subendothelial layer where they terminate as arborizations. That these fibers are carried by the vagus is based on the fact that the plexus in which they occur is formed by a branch from this nerve.

The nerve bundles that contain afferent fibers which end in the walls of the left pulmonary veins arise from the plexus on the posterior-lateral surface of the wall of the left atrium. This plexus receives afferent fibers from the right cardiac nerve, which emerges from the vagus at the level of the inferior cervical ganglion; and from one of the two left sympathetic cardiac nerves, which receive branches from the left vagus. Branches from the same plexus may supply the right pulmonary veins or they may receive fibers from other sources.

Having no other definite information Michelazzi (1933) suggested that the great number of nerves in the venae cavae and pulmonary veins indicate that some of the endings of these fibers are sensory in nature, and these veins play an important role in regulating circulation.

Nonidez (1937), using a silver nitrate method of impregnation, showed that afferent endings are stained from dark brown to deep black depending on the diameter of the fiber. Arborizations of thinner fibers are most sharply stained. By applying these staining methods to newborn and young dogs, Nonidez observed the presence of afferent nerve endings in the intrapericardial portions of the venae cavae and pulmonary veins. He distinguished two types of sensory endings. The first type consists of nerve endings which resemble the pressoreceptors in the walls of the carotid sinus, right subclavian artery, and the arch of the aorta. Nerve endings of the second type are found in the walls of the pulmonary veins.

The subendothelial arborizations occur in the walls of the venae cavae and pulmonary veins, they have also been found, though very rarely, in the walls of the coronary sinus. Due to the lack of thickness of the subendothelial layer these nerve endings appear to be flattened. Their branches are parallel to the endothelium. The fibers from which they arise are thick, and after crossing the myocardial portion of the wall of the veins, run for some distance in the subendothelial layer before ending. The subendothelial endings in the pulmonary veins are smaller than in the venae cavae although they perform identical functions. The arborizations are variable. Some endings are small and

compact, others occupy a large area. The nerve terminations have reticulated swellings along their branches. These swellings are also found in the forementioned presoreceptors. The branches of the subdenothelial endings often appear wavy. This wavy, twisted appearance is due to contraction of the vein walls. The subendothelial endings appear closely placed in newborn and young animals. In adult animals they are more scattered. Nonidez (1937) was unable to see ganglion cells in the subendothelial layer of any large veins, or in the myo cardial fibers of these vessels. This would disprove any possibility that the branches may be dendrites from multipolar cells.

In the walls of intrapericardial portions of the pulmonary veins, there is another type of nerve aborization that is closely associated with cardiac muscle fibers. These aborizations originate from large fibers which run along the wall of the vein for some distance before breaking up into branches. Some fibers end in terminal rings. A good example of this would be found in the young kitten. There are other fibers which end as large, small or flattened reticulated enlargements.

The areas of distribution of the sensory nerve endings in the intrapericardial portions of the venae cavae and pulmonary veins offer a strong suggestion that they originate the nerve stimuli that results in Bainbridge's reflex. Bainbridge (1916) working with dogs found that injecting fluid or blood through the jugular vein caused a rise in venous pressure and a speeding up of the heart. After sectioning the vagus nerves the acceleration of the heart disappears. Bainbridge came to the conclusion that the heart is provided with a reflex mechanism whereby, when the venous filling is increased, the circulation can be maintained by a rapid transference of blood from the venous to the arterial system. By this mechanism, the risk of excessive dilation and of failure of the heart is lessened. This reflex mechanism must play a part in the quickening of the heart during muscular exercise. During exercise there is increased venous inflow to the heart and a rise in venous pressure. There are no afferent nerve endings in the walls of the jugular veins, the extrapericardial portions of the superior vena cava and most of the wall of the inferior vena cava. These parts of the venous system are not directly involved in Bainbridge's reflex.

E. Somatic Sensory Innervation

Fulton (1947a) explained that practically all the

vasoconstrictor neurons belong to the sympathetic division of the autonomic nervous system. Vasodilator neurons are not confined to the parasympathetic system. In addition to these, a group of vasodilator fibers leaves the spinal cord in the thoraco lumbar region mingled with the preganglionic vasoconstrictor fibers. A third group of vasodilator fibers is found in the somatic division of the nervous system. The neurons of the first two groups are efferent, while the neurons of the somatic system which cause vasodilation are afferent. Their cell bodies are located in the spinal ganglia. Somatic vasodilator fibers reach the blood vessels in the skin of the extremities through the posterior spinal roots.

Stricker (1876) working with dogs, discovered that stimulating the dorsal roots of the spinal segments which contribute to the sciatic nerve, results in a temperature rise and a reddening of the foot. Bayliss (1923) carried out this experimentation further, and found that by stimulating the dorsal roots of the fifth, sixth and seventh lumbar and first sacral nerves, there results a reddening of the skin, a temperature rise in the toes, and an increase in the volume of the hindlimbs. Bayliss demonstrated that these fibers from the dorsal root ganglia are similar in structure and course to ordinary sensory nerve fibers. He believed they were identical, and that impulses carried by them

brought about vasodilation of the skin vessels.

Bayliss showed that vasodilation of the vessels of the skin of the extremities by way of the dorsal roots results reflexly by stimulating the depressor nerve. Therefore, there appears no reason for doubting the vasodilator nerves of the dorsal root play a part in regulating the blood vessels in the skin of the extremities.

F. Visceral Afferent Innervation

The visceral afferent nerves are the sensory components of reflex arcs which control visceral vascular phenomena. The functions of the visceral afferents can be observed in the cardiac reflexes, and in the aortic and carotid sinus reflexes. These reflexes have been explained in some detail individually.

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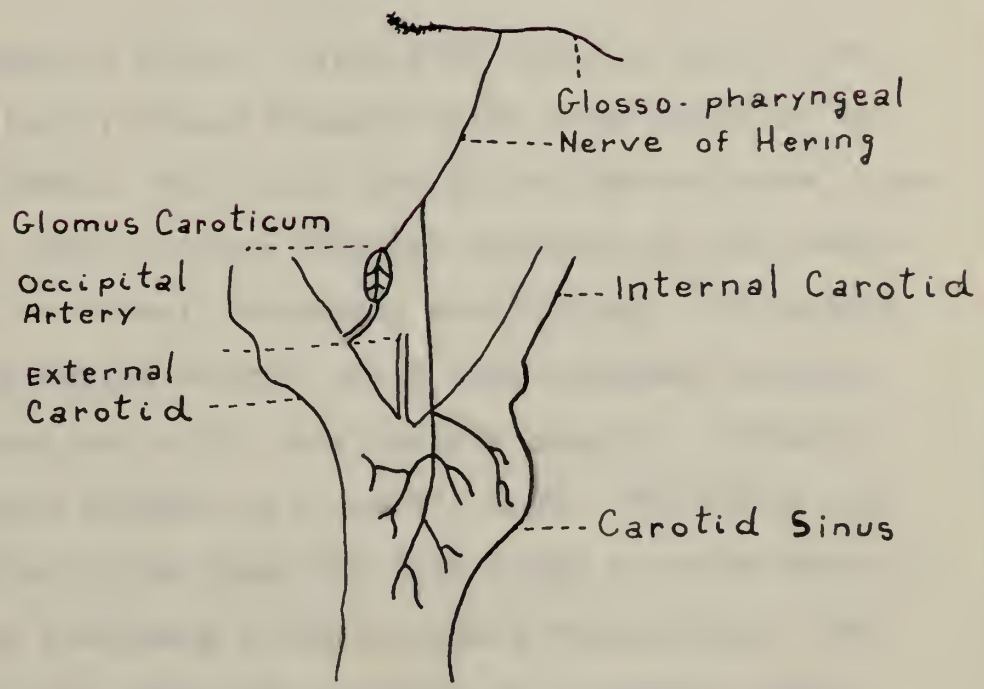


Figure IV

THE CAROTID SINUS MECHANISM OF THE RABBIT - Daubrebande (1934)

IV. RELATIVE INNERVATION OF VARIOUS PARTS OF VESSELS AND SYSTEMS

Woollard (1926) listed five types of myelinated nerve endings in blood vessels which were described by Lapinsky (1905). The first type of myelinated nerve loses its sheath some distance from its termination and eventually ends in a freely branching termination. The second type has branching endings which form terminal brushes. These brushes may be of considerable length. Lapinsky likened these brushes to a comet's tail. The third type of myelinated nerve gives off tiny twigs at right angles. These twigs terminate in small knobby thickenings. The fourth type of nerve ends abruptly in a granular like ending. The fifth type, which is an indeterminate form, branches and appears to end in large oval swellings.

Woollard confirmed the statements of Lapinsky and in addition made several observations of his own. His experimentation consisted of removing the left abdominal sympathetic trunk from cats, tracing the paths taken by the myelinated (sensory) nerve fibers, and by studying how these nerves terminate peripherally.

In observing the left anterior tibial artery of the cat, Woollard was able to find in the tissue adjacent to the artery and under the deep fascia, a nerve trunk consisting of three fibers (figure V). Two of these fibers are large myelinated fibers. The middle fiber is much finer. One of the myelinated fibers gives off a myelinated side branch. This divides into two fibers which are thick and myelinated. Each of the terminating branches ends in a Pacinian corpuscle lying in the fat tissue. Inside the corpuscle, the end fiber becomes unmyelinated and forms a terminal tuft of fibers at its extremity. Woollard believed that although these sensory endings are a short distance from the blood vessel, they are close enough to be regarded as fibers which may be concerned with reflexes of the "axon reflex" type.

Woollard traced the main nerve trunk from which the branches arise, along the course of the blood vessel. It's final distribution could not be detected.

In the anterior tibial artery of the cat, there is an arrangement that, according to Woollard, seems "universal in the distribution of sensory nerves in the neighborhood of the vessels." It applies to veins as well as to arteries. This arrangement is illustrated in (figure VI). The main nerve trunks run along the course of the arteries. From a main trunk there arises a thread of nerves which consists

of two or three myelinated fibers. These nerves run along the blood vessel, and then loop around and cross the vessel. They then join similar fibers from the nerve trunk. The origin of these fibers may be either a short or long distance from the origin of the preceding thread. Some of the fibers pass to their distribution by this means. By this winding and coiling there is a continuous plexus of myelinated nerves running along the longitudinal axis of the vessel. The myelinated nerves which wind around the vessel, by giving off collaterals are not only associated with the vessel wall but also with the neighboring connective tissue. These nerves terminate in the adventitia of the vessel, in the adjacent adipose tissue, in the dense facia, or in the sheath of the adjacent musculature. In the adventitia of the vessel wall, the nerve endings are naked axis cylinders which grow continually finer and give off small blunt lateral enlargements. The fine subdivisions become beaded. These endings in the adventitial wall are of Lapinsky's types one, two, and three.

In addition to the sensory endings of myelinated nerves in the adventitia, and the collateral endings in the adjacent tissues, there are myelinated nerves which can be traced from the adjacent nerve trunk, through the adventitia until they reach the muscular coat. In the muscular layer

the nerves become unmyelinated. By repeated branching they form small beaded fibers which cannot be distinguished from the plexus located in the muscular layer, formed by nerves from the sympathetic chain (figure VII). This type of sensory ending is rarily seen. For the most part myelinated fibers terminate between the adventitia and tunica media.

In the femoral artery ofthe rabbit, Woollard found endings of myelinated nerves which are structurally identical with depressor endings. These complex endings of densely myelinated nerves are found near the tunica media. They are much more dense and complicated than the other myelinated endings seen so far. They have not been found in the peripheral blood vessels of other animals.

A. The Innervation of Capillaries

Capillaries are regularly accompanied by nerves. The nerve fibers are unmyelinated, and run along either side of the vessel. They cross the capillary and show small swellings at irregular intervals. Ganglion cells have not been found. Actual connection with the capillary wall has not been confirmed.

Hinsey (1928) showed very clearly that in skeletal muscle preparations of the cat there are small sensory

myelinated fibers. The fibers travel in the adventitia of the blood vessels and their unmyelinated branches terminate in the adventitia of these vessels. They were not found in relation with capillaries, but were traced up to the terminal arterioles. They even appeared at the junction of the terminal arterioles and the capillaries. This however, was difficult to confirm absolutely. Hinsey was also able to observe branches from myelinated fibers terminating in the adventitia of the small veins and venules. He also saw branches terminating in the adipose and connective tissue surrounding these small blood vessels.

Although no actual sensory endings have been observed in capillary walls, it was shown by Doi (1920) and confirmed by Krogh, Harrop and Rehberg (1922) that a large number of capillaries in the web of the frog's hind leg will respond to stimulation of posterior roots. To show that a dilation of arteries cannot be responsible for this capillary reaction, Doi (1920) applied a dose of acetyl choline. This drug causes a maximal dilation of arteries and prevents any response by the arteries when the nerves are stimulated. The dilation in this case therefore must be due to capillaries alone. Similar experiments were done by Langley (1921) upon the cat's paw.

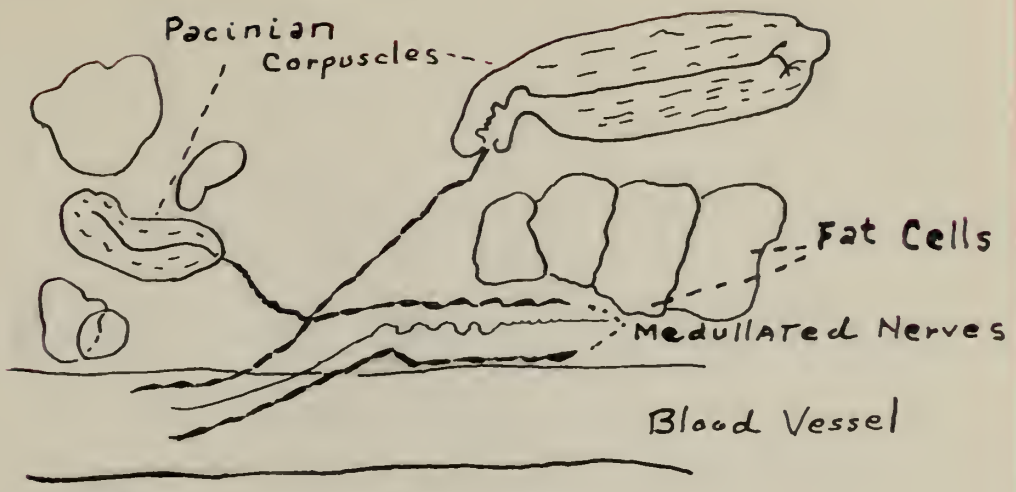
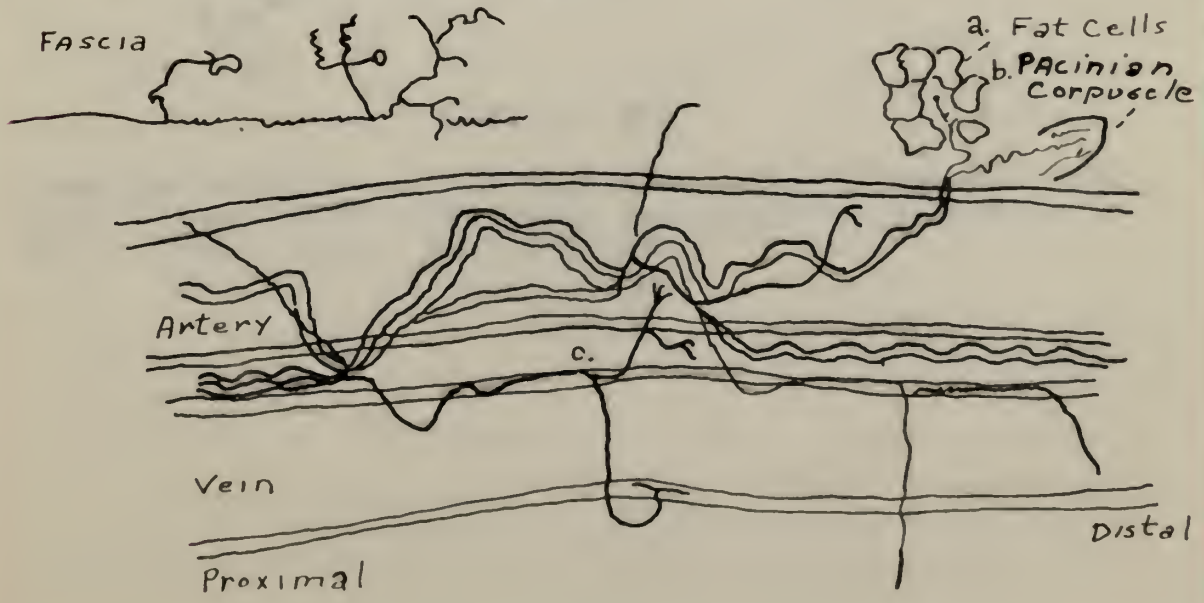


Figure V

A COLLATERAL OF A MYELINATED NERVE RUNNING ALONG A BLOOD VESSEL ENDING IN PACINIAN CORPUSCLES - Woollard (1926)

Figure VI

SKETCH OF THE INNERVATION OF THE LEFT TIBIAL ARTERY IN A CAT. The left abdominal sympathetic trunk had been removed. Myelinated nerves form an investing plexus which ends (a) in free endings in the adjacent connective tissue and fat cells (b) in a Pacinian corpuscle; (c) in the adventitia of the blood vessel. - Woollard (1926)



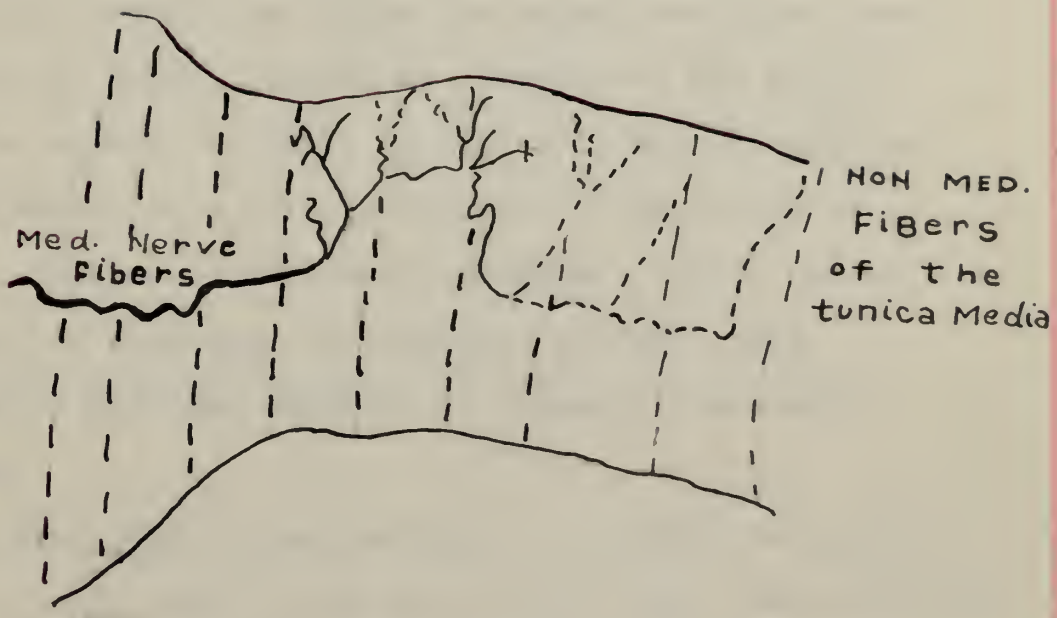


Figure VII

A myelinated nerve ending in a fine non-myelinated plexus which begins in the adventitia and reaches the muscular coat. Normal cat. - Woollard (1926)

V. GENERAL PHYSIOLOGICAL CONCEPTS

A. Evidence for Segmental Innervation of Blood Vessels

The parts of vasomotor neurons, dilator as well as constrictor, which lie within the spinal cord have been described by Fulton (1947a) as elements of the spinal vasomotor center. He feels justified in his description because "there is a certain amount of integration of afferent impulses which occurs at spinal levels before the impulses are expressed in vasomotor action." This integration has been observed in segmental vasomotor reflexes.

Lovén (1866) experimenting with rabbits described a reflex of this type in the ear and hind leg. These reflexes are called Lovén reflexes. Since this time many similar reflexes have been observed, and in general it may be stated that when there is a stimulation of an afferent nerve from any organ, a general rise in blood pressure is produced, partly due to vasoconstriction. At the same time a local vasodilation in the organ itself is produced.

As an example of the dilation, the work of Bayliss (1900-1) can be cited. He showed that vasodilation which

results from stimulating the aortic depressor or carotid nerves results not only in inhibiting the vasoconstrictor mechanism as imagined by Cyon and Ludwig (1866) but also in stimulating a vasodilator mechanism.

Bayliss cut the posterior roots of the dog, and still obtained a dilation. This showed that there was an inhibition of the normal constrictor tone. To prove that both processes are concerned, he sectioned the cervical sympathetic which supplies the vasoconstrictors and demonstrated a vasodilation mechanism in the submaxillary gland.

B. Types of Endings

1. Pressoreceptors and Chemoreceptors in the Carotid Sinus and Carotid Body.

Histological studies by DeCastro (1927-28) failed to show pressoreceptors in the walls of the carotid artery above or below the carotid sinus. Comroe and Schmidt (1938) placed ligatures around the external carotid artery of the cat between the origins of the carotid sinus and the occipital artery, and separated the pressoreceptors from the carotid body circulation. They found that pressure changes of 200 mm. on the carotid body side of the ligature were ineffective. Comroe and Schmidt thus provided physiological evidence that pressoreceptors are excluded from the carotid body segment. Winder, Bernthal, and Weeks (1938) anes-

thetized dogs, and separated the carotid sinus pressoreceptors from the carotid body by completely isolating the arterial bifurcation, and by using ligatures.

The carotid body is a part of a system of cell groups called chromaffine bodies, paraganglia, glands, nodules and glomera. Anatomists have observed these bodies close to the main arteries, but the junction between them was practically unknown, until the discovery of the carotid sinus reflexes which opened new fields for investigation that had previously been unsuspected. The major function of the carotid body, and probably its only function, according to Schmidt and Comroe (1940) is now known to be due to the presence within it of chemoreceptors. Chemoreceptors are nerve endings that are specialized to respond to certain changes in the chemical composition of their environment (which is arterial blood). These changes give rise to reflexes which can produce physiologically important effects upon respiration and circulation. The chemoreceptors are affected by such stimuli as asphyxia, anoxia (due to reduced oxygen pressure in the arterial blood or by poisons such as cyanide by which cell oxidation is inhibited), acidosis and drugs which have "nicotinic" properties.

DeCastro (1927-8) described the structure of the carotid body as being unusual in that afferent arteries open into sinusodial spaces. These spaces are lined with

endothelium and "glomus cells." These glomus cells contain a rich supply of nerve endings. Schmidt (1932) furnished evidence that chemoreceptors are located in the carotid body. He ligated the occipital artery at its origin in dogs. This reduced or abolished the reflex effects of altering the gas content of the blood in the carotids. Comroe and Schmidt (1938) injected small doses of lobeline or cyanide into the carotid arteries. The effects of these drugs were entirely abolished, when the small artery to the carotid body was clamped. When this vessel was opened the effects were restored. Comroe and Schmidt showed, in this experiment, that the carotid body is the only location of importance for chemoreceptors in this region. Comroe and Schmidt experimenting on dogs indicated that pressoreceptors can be demonstrated by means of action potentials in any preparation in which chemical sensitivity is retained. This holds true even when the fibers running from the carotid sinus to the carotid body are completely stripped away, and the external carotid denuded and ligated between the internal carotid and the occipital artery. The number, and physiological importance of these receptors is questionable. This opens the possibility that there are chemoreceptors in the pressoreceptor area of the carotid sinus. If this is true,

it has not been revealed by methods used so far to detect it.

2. Pressoreceptors and Chemoreceptors in the Aortic Arch, Subclavian Artery and Glomus Aorticum

The pressoreceptors of the arch of the aorta in new born and young animals are of relatively simple structure. However, even at these stages some of them have a dense arborization. Nonidez (1941) observed that in older animals the pressoreceptors are more complex and resemble the functionally identical nerve endings of the carotid sinus.

Nonidez surmised that perhaps the number of aortic pressoreceptors are determined some time before birth; since it is during the embryonic period that afferent nerve fibers enter the wall of the aorta. He feels that it is questionable whether there are new arborizations in the late fetal period and most improbable that they develop in the postnatal period. The pressoreceptor area is very apparent at birth, and the nerve endings are closely placed.

The pressoreceptors of the dog vary in diameter. Thus far it is not possible to make accurate measurements,

because with the technique used, the myelin is completely dissolved. The thicker axons which have their endings in the wall of the aorta often have a beaded appearance because of postmortem contraction of the wall. This is further exaggerated by shrinkage that takes place in the preparatory technique of the sections.

The aortic pressoreceptors differ from those in the carotid sinus in that they branch in the outer third of the media among the elastic membranes and the smooth muscle fibers of this layer. This also applies to the pressoreceptors of the subclavian artery.

There are distinct swellings along the branching nerve endings. The swellings may be terminal or may be located at any point along the branch. These swellings are more developed in rabbits than in dogs.

According to Nonidez (1941) the branches terminate in variable arborizations. Some end as reticulated enlargements, others as large, compact club-shaped swellings, or as single or double rings of various sizes.

Nonidez also pointed out that in close proximity to the endings of the pressoreceptors, there is an abundance of nuclei. He was uncertain as to the nature of these cells, but suggests that since they occur in contact with, or close to the endings, they may release substances concerned

with the metabolism of the neuron.

The pressoreceptors function constantly during the heart cycle. They are even stimulated by changes in blood pressure incidental to systole and diastole. The thin afferent fibers terminate differently than the large and medium sized fibers. The branches lack reticulated swellings or, if they are present, they are poorly developed.

Monidez (1935a) showed that endings of pressoreceptor type also occur in the externa of the small arteries that supply the aortic bodies. He found them in some instances in the wall of the aorta, near the base of these arteries.

The position of most of the pressoreceptors in the wall of the aorta may cause these pressoreceptors to have a lower threshold of excitation than those of the carotid sinus, since they lie among the closely placed elastic membranes of the outer third of the media. Bauer (1930) supported this view. The aortic depressor reflex in the rabbit can first be noted at a pressure of 65mm. Hg. The carotid sinus reflex commences at a pressure of 80 mm. Monidez (1935a) stated that the more dense, compact arborizations arising from thin fibers might be affected only by higher pressures. They may be emergency presso-receptors. None of this has been proven experimentally.

Heymans, Bouckaert and Dautrebande (1931) found that the pressure sensibility for the carotid sinus receptors of the dog is within the range of 85 to 110 mm. Hg. Above 110 mm. there is a reflex fall in blood pressure and bradycardia. The same situation exists below 85 mm. except that hypotension in the carotid sinus causes a rise in blood pressure and tachycardia. Between 0 and 50 mm. an increase in pressure leads to hypertension, while a decrease causes hypotension.

This innervation of reflexes at low pressures has been explained by Heymans et al, as due to the collapse of the sinus wall. This collapse causes shortening of the connective tissue fibers, which in turn impinge on the branches of the nerve endings. These endings, thus excited, cause hypotension and bradycardia. If the blood pressure is increased, the compression on the pressoreceptors is lessened, the blood pressure rises and the heart is speeded up. This illustrates the mechanical nature of stimulation of the pressoreceptors.

The aortic pressoreceptors are essentially the same as the carotid sinus pressoreceptors in structure and in function. The histology and gross anatomy of the aortic body is very similar to that of the carotid body. Boyd (1937) explained that embryologically the carotid

body originates from the mesoderm of the third branchial arch artery and the ectoderm of the glossopharyngeal nerve. The aortic body is of similar origin from the fourth left branchial arch artery and the vagus nerve.

The blood supply of the aortic body comes from a branch of the transverse aorta in the dog, and from the coronary arterial system in the cat.

Comroe (1939) explained the localization of chemoreceptors in the aortic body. He injected cyanide or lobeline into the aorta through a small catheter which could be moved in and out, and demonstrated that the chemosensitive area in dogs lies at a point at which a small artery leaves the aorta to enter the aortic body. Comroe was also able to identify a nerve leading from this region to the vagodepressor trunk. He stimulated this nerve electrically and produced effects exactly like those which are produced by chemical stimulants. In another experiment Comroe crushed the nerves in the vicinity of the aortic body. By doing this, he abolished chemoreceptor activity in the aorta. Some of the pressoreceptor function, however was retained.

The nerves from the aortic body of the dog join the vagodepressor trunk in the region where the recurrent laryngeal nerves on the right and left side emerge. Sometimes the afferent nerve from the aortic body can be

isolated and stimulated. It can be identified only by its physiological effects. Increased activity of the chemoreceptors of the carotid and of the aorta brings about an increase in the activity of the respiratory and vasomotor centers. Decreased activity of these chemoreceptors brings about opposite effects.

It has been suggested that circulation is influenced primarily by impulses from the pressoreceptors while the respiratory center is most powerfully influenced by impulses from chemoreceptors.

3. Pressoreceptors in the Large Veins of the Heart

In comparing the receptors in the large veins, with the pressoreceptors in the carotid sinus, the right subclavian artery, and the aortic arch, certain differences are noted. The pressoreceptors of the carotid sinus occur in the externa; those of the right subclavian, and arch of the aorta occur in the externa and outer third of the media. In the large veins they are found in the subendothelial layer. Nonidez (1941) states that this difference is not of too much importance since the blood pressure in the large veins is normally far below the pressure in the arteries. The aborizations among the elements of the loose connective tissue under the endo-

thelium are extremely sensitive to slight changes in intravenous blood pressure. According to Nonidez (1937) the structure of the large subendothial endings in these large veins does not differ from the structure of the pressoreceptors of the arteries.

Sassa and Miyazaki (1920) showed that Bainbridge's reflex can be brought about by distending the right auricle with a rubber balloon attached to a tube. This distension causes a rise in venous pressure. The authors believed that this rise of pressure was due to stimulation of the pressoreceptors in the venae cavae; for according to their observations there were no pressoreceptor type endings in the walls of the auricles. Sassa and Miyazaki also observed that if the left auricle was distended, the heart was accelerated but there was no rise in venous pressure in the right auricle. Nonidez (1937) attempted to explain this by suggesting that the pressoreceptors of the pulmonary veins would bring about Bainbridge's reflex in this case; because increased blood pressure in these veins would undoubtedly affect the rate of the heart. This suggestion needs experimental verification.

Since reflex acceleration of the heart does not take place after the vagi are sectioned, it is quite obvious that afferent fibers run in these nerves. It is difficult

to trace these fibers to the subendothelial layer for there is a plexiform arrangement of sympathetic, parasympathetic, and cerebro-spinal afferent fibers in the same bundle.

McDowall (1935) observed a cardiopressor nerve in cats. Nonidez (1937) suggests that this nerve contains the sensory fibers which terminate as pressoreceptors in the venae cavae. This nerve arises from the right vagus at the level of the right subclavian artery. When it is stimulated it causes a rise of pressure. At this same level if the main trunk of the vagus is centrally stimulated, a depression is caused. McDowall (1935) states, "The fact that section of the vagus in the neck prevents a rise of blood pressure, and that such section, after previous section of the trunk of the vagus below the branch causes a fall of blood pressure, suggests that the afferent pathway of the vago pressor reflex is the cardiopressor nerve."

It was explained previously that the large plexus between the venae cavae arises partly from the branch of the right vagus. The myelinated fibers which end in the walls of the venae cavae run in this plexus. Nonidez (1937) stated that if this nerve is directly stimulated, a rise in blood pressure occurs through acceleration of the heart. This is identical with Bainbridge's reflex. Thus physiological and anatomical evidence for Bainbridge's reflex in

the venae cavae has been found. Experimental evidence must still be given for Bainbridge's reflex in the pulmonary veins.

4. Pressoreceptors of the Splanchnic Circulation

Nonidez (1947) searched for an anatomical basis for the physiological pressoreceptor response described by Heymans and coworkers (1936) in the splanchnic circulation of the dog. After denervation of the carotid sinus and aortic arch, an increase in the general blood pressure still produced vasodilation, and a decrease produced vasconstriction in the splanchnic circulation. Using the silver nitrate staining method of Cajal, with chloral hydrate as a fixative, Nonidez reported that pressoreceptors occur at the bases of the coeliac and superior mesenteric arteries. The pressoreceptors are terminations of medium sized nerve fibers branching in the externa as well as in the outer half of the media of these arteries. The branches of the terminal arborization are longer than those of the carotid sinus and the aorta, and do not possess reticulated swellings. Nonidez has not been able to find arborizations of this type in the descending aorta, or in the renal, inferior mesenteric and spermatic arteries. He has not determined the origin of these fibers, but assumed that they reach their destination by way of the splanchnic nerves and the coeliac plexus.

Nonidez bases this assumption on the report by Heymans and coworkers (1936) that the splanchnic vascular reflexes are abolished after destruction of the spinal cord.

S U M M A R Y

The sensory innervation of the blood vascular system has been widely investigated. Anatomists and physiologists, as a result of observations from research, have brought forth evidence for this innervation. The evidence can be summarized as follows:

(1) The axon reflex involves a dilation of skin vessels confined to the region of stimulation. Impulses pass toward the center along sensory fibers, and towards the periphery along vasodilator fibers to the smaller vessels, causing their dilation.

(2) When sensory fibers are stimulated at their central ends, a dilation of vessels occurs at their peripheral ends in the tissues of the body. Dilation of this kind can be explained by antidromic conduction.

(3) The blood vessels of the skin are regulated by axon reflexes, and by local and general reflexes.

(a) The bright red flare that normally follows a localized injury to the skin is due to an axon reflex.

(b) A local reflex takes place partly through vasodilator nerves which have their pathway in the

antero-lateral region of the spinal cord, and partly by inhibiting vasoconstrictor impulses. Such reflexes are known as "Lovén reflexes."

(c) The general reflexes give rise to general vasoconstriction. General vasoconstriction is a reflex response to stimulation of the central ends of sensory nerves.

(d) Cutaneous vessels have been considered to be innervated by sensory nerves that act antidromically.

(4) Evidence for the sensory innervation of blood vessels in various tissues and organs has been presented.

(a) Visceral afferent fibers have been observed in association with the blood vessels of the kidney, the liver, the myometrium of the human uterus, and the spleen.

(b) The blood flow to the viscera is controlled in essentially the same fashion as blood flow to the skin. Myelinated visceral afferent fibers have been seen in assocation with blood vessels of all of the viscera. The blood flow is regulated by axon reflexes, segmental reflexes of the Lovén type, and by the vasomotor centers of the central nervous system.

(c) Unmyelinated branches of myelinated nerves have been observed passing to the adventitia of arterioles in skeletal muscle.

(d) There are sensory terminations in the adventitia of the pulmonary arteries in the rabbit. These endings have been found only near the base of the artery close to the hilum of the lung.

(e) In the pia mater of the brain, large myelinated nerve fibers have been observed accompanying the blood vessels at the base of the brain, the medulla, and over the cerebrum to the great longitudinal fissure. Myelinated fibers have also been found in the tela choroideae. Unmyelinated branches of myelinated nerves have been observed accompanying the vessels of the dura.

(5) The carotid sinus is the source of afferent impulses which exert important reflex effects in the regulation of circulation, and respiration. Variations of the intra-sinus pressure play a part in the regulation of the general blood pressure. Hypertension in this region produces general somatic hypotension with bradycardia, while a reduced intracarotid pressure in general hypertension by means of peripheral vasoconstriction and tachycardia. The carotid sinus mechan-

may be evolved from a phylogenetic elasmobranch-like ancestor by delimitation of the widespread reflex areas to derivatives of the branchial arches.

(6) Myelinated (sensory) fibers have been found in the subpericardial and endocardial tissues as well as in the valves of the heart. There are also plexuses in the adventitia of the aorta, pulmonary arteries, and in the tissues that surround the coronary arteries. The plexuses of afferent nerves are rich in the auricles, but not as compact in the ventricles.

(7) The aortic depressor nerve is a bundle of afferent fibers mediating impulses, originated through changes in blood pressure, from the aortic territory to the nerve centers. When the Aortic nerve is stimulated by reflex dilation there is a fall in blood pressure, while increased blood pressure is caused by vasoconstriction.

(8) Abundant sensory nerve endings (pressoreceptors) have been found in the intrapericardial portions of the venae cavae, and pulmonary veins. There are also endings in the wall of the coronary sinus as it opens into the atrium. These pressoreceptors may originate the stimuli that result in Bainbridge's Reflex.

(9) Sensory endings of myelinated nerves have been traced to the adventitia of arteries and veins. In the adventitia the myelinated fibers become naked axis cylinders. These fibers grow continually finer and give off small blunt lateral enlargements. Many myelinated fibers terminate between the adventitia and the tunica media. Collateral endings have been seen in the adjacent fatty tissue, in the dense fascia, and in the sheath of the adjacent musculature. In the fat tissue, branches of myelinated fibers have been seen ending in Pacinian corpuscles.

(a) Branches from myelinated fibers have been observed terminating in small arteries, veins, arterioles, and venules. Actual sensory endings in capillary walls have not been observed.

(10) The function of the carotid body is known to be due to the presence within it of chemoreceptors. Pressoreceptors in the aortic arch and right subclavian artery; and chemoreceptors in the aortic body are similar in function to those of the carotid sinus and carotid body. Evidence has been presented for the existence of pressoreceptors for the splanchnic circulation in dogs.

- A B S T R A C T -

This is a review of the literature, in which anatomical, and physiological evidence for the sensory innervation of the blood vascular system is presented.

On commencing this study of the innervation of blood vessels by sensory nerves, mention is made of the possibility of an axon reflex. The axon reflex involves a dilation of skin vessels confined to the region of stimulation. Impulses pass toward the center along sensory fibers, and towards the periphery along vasodilator fibers to the smaller vessels causing their dilation.

If the sensory fibers are stimulated at their central ends, a dilation of vessels occurs at their peripheral ends in the tissues of the body. Dilation of this type has been explained by antidromic conduction.

Several authors have observed myelinated (sensory) nerves innervating the blood vessels in various tissues and organs. From their observations they have concluded that the blood vessels of the skin are regulated by axon reflexes and by local and general reflexes. Some investigators also believe that the cutaneous blood vessels are

innervated by sensory nerves that act antidromically.

Sensory fibers have been seen in mammals in assocation with the blood vessels of the kidney, the liver, skeletal muscle, the uterus, the spleen, and with all of the viscera. There are endings of myelinated fibers in the adventitia of the pulmonary arteries. These endings have been observed only at the base of the artery close to the hilum of the lung of the rabbit. In the pia mater of the brain in the dog, cat, and rabbit, myelinated nerve fibers accompany the blood vessels at the base of the brain, the medulla, and over the cerebrum to the great longitudinal fissure. The richest supply of fibers have been found in the tela choroideae. Those are also myelinated fibers accompanying the vessels in the dura.

In the heart there are fine myelinated plexuses in the supericardial and endocardial tissues, as well as in the valves. They innervate a portion of the heart that is non-muscular, and are therefore considered to be sensory. Plexuses have also been found in the adventitia of the aorta, pulmonary arteries, and in the tissues that surround the coronary arteries.

The sensory mechanism of the carotid sinus exerts important reflex effects in the regulation of circulation and respiration. Variations of the intrasinus pressure play

a part in the regulation of the general blood pressure. An increase in the pressure of the sinus affects the sensory endings (pressoreceptors), and causes a fall in blood pressure. If the sinus pressure is decreased, a rise in blood pressure follows. When the general blood pressure is increased, the respiration is also increased. The carotid sinus mechanism may be evolved from a phylogenetic elasmobranch-like ancestor by delimitation of the widespread reflex areas to derivatives of the branchial arches.

When the nerve endings of the aortic nerves (depressors) in the wall of the aorta, or at the base of the right subclavian artery, are stimulated, reactions that are identical with those of the carotid sinus occur. Evidence for the existence of pressoreceptors for the splanchnic circulation in dogs has been presented.

Sensory endings, similar to the aortic, and carotid sinus pressoreceptors, have been found in intrapericardial portions of the venae cavae and pulmonary veins in dogs. These fibers emerge from branches of the vagus. The areas of distribution of these sensory nerve endings, offer a strong suggestion that they originate the nerve stimuli that results in Bainbridge's reflex. This is a reflex mechanism whereby, when venous filling is increased, the circulation can be maintained by a rapid transference of blood from the

venous to the arterial system. This mechanism may play a part in the quickening of the heart during muscular exercise.

When the paths taken by myelinated fibers are traced to blood vessels; veins as well as arteries, they are seen to run along the vessel,then loop around and cross the vessel. These nerves, by giving off collaterals are not only associated with the vessel wall, but also with the neighboring connective tissue. The nerves terminate in the adventitia of the vessel or between the adventitia and the tunica media, in the adjacent fatty tissue, in the dense fascia, or in the sheath of the adjacent musculature. Unmyelinated branches from myelinated fibers have been seen to enter Pacinian corpuscles. The collateral nerve endings in blood vessels, adjacent fatty and connective tissue, may be the anatomical evidence for the axon reflex. Unmyelinated branches from myelinated fibers have been traced to the adventitia of arterioles and venules. They even appeared at the junction of the terminal arterioles and the capillaries. This, however, was difficult to confirm absolutely. No actual sensory endings have been observed in capillary walls.

When there is a stimulation of an afferent nerve from any organ, a general rise in blood pressure is produced, partly due to vasoconstriction. At the same time a

local vasodilation in the organ itself is produced. Reflexes of this type are known as Lovén reflexes.

The function of the carotid body and the aortic body is known to be due to the presence within them of chemoreceptors. Chemoreceptors are sensory nerve endings that are specialized to respond to certain changes in the chemical composition of their environment (which is arterial blood.) These changes give rise to reflexes which can produce physiologically important effects upon respiration and circulation.

That much more research is needed in the study of the sensory innervation of blood vessels, is very evident. New staining techniques, and modifications of the present ones must be developed for following myelinated nerves to their final terminations; and new physiological methods must be perfected.

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